#24
10-23-01

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicants	:	Balin et al.
Serial No.	:	09/227,749
Filed	:	January 8, 1999
For	:	Treatment and Diagnosis Of Alzheimer's Disease
Group Art Unit	:	1200
Examiner	:	Eli Peselev

DECLARATION OF DR. J. TODD ABRAMS

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

1. I, Dr. J. Todd Abrams, PhD, one of the named inventors in the above application, make this Declaration in support of the patentability of the above invention. All statements made herein are made under penalties of perjury.

2. Attached as Exhibit A hereto, is a true and correct copy of my curriculum vitae.

3. I have reviewed all of the Office Actions and cited references in the above patent application and am familiar with them.

4. The present invention relates to a method of treating Alzheimer's disease by administering a therapeutic amount of an anti-microbial agent, alone, or in

combination with an anti-inflammatory agent. There is nothing in the cited prior art which shows or suggests the presently claimed invention.

5. Attached as Exhibit B to this Declaration is a true and correct copy of a series of unsolicited letters which I have received, describing the clinical course of their loved ones or patients after they were placed on antibiotics for an extended period of time for the treatment of Alzheimer's disease. As shown in the attached letters, some of these individuals had dramatic improvement that is documented in some cases with the inclusion of medical records. Certain identifying information has been removed from these letters for privacy concerns.

6. These types of reports stimulated our interest in beginning our own clinical trial on the present invention. We have begun a pilot clinical trial with patients with diagnosed Alzheimer's disease being placed on antibiotic for a 6-month period of time. These patients were given azithromycin (xxx mg/day) for a period of 6 months.

7. Preliminary results are shown in attached Exhibit C and indicate that these 3 patients remained stable during this period of time (which is the goal of the study). Study results of three patients who were tested with a battery of standard tests for cognitive function accepted by the medical community indicate that these three patients remained stable during the trial period of the present invention.

8. The two standardized tests the patients were subjected to were the MMSE (Mini Mental Status Exam, for cognitive function) and the AMPS (Assessment of Motor and Processing Skills). The AMPS has been fully standardized internationally and cross-culturally on more than 25,000 subjects. In the charts shown in Exhibit C, the column entitled "GDS" refers to Geriatric Depression Scale.

9. In the AMPS test column of Exhibit C, the line entitled "Motor" refers to skills such as: Stabilizes, Aligns, Positions, Walks, Reaches, Bends, Coordinates, Manipulates, Flows, Moves, Transports, Lifts, Calibrates, Grips, Endures and Paces. These motor skills are observable goal-directed actions the person enacts during the performance of ADL tasks in order to move oneself or the task objects.

10. In the AMPS test column of Exhibit C, the line entitled "Process" refers to cognitive processing skills such as: Paces, Attends, Chooses, Uses, Handles, Heeds, Inquires, Initiates, Continues, Sequences, Terminates, Searches/Locates, Gathers, Organizes, Restores, Navigates, Notices/Responds, Accommodates, Adjusts and Benefits. These process skills are the observable actions of performance the person enacts to logically sequence the actions of the ADL performance over time, select and use appropriate tools and materials, and adapt his or her performance when problems are encountered.

11. In the AMPS test column of Exhibit C, the column entitled "Task 1" and "Task 2" refer to the two Activity of Daily Living Tasks chosen in order to evaluate the quality of the person's motor and process skills as they are manifested in the context of the ADL task performance. The ADL tasks include self-care, personal activities of daily living (PADL), as well as domestic or instrumental activities of daily living (IADL). The subject can choose from a list of 76 tasks which are all rated in degree of difficulty.

12. In the AMPS test column of Exhibit C, the numbers are based on scoring each of the tasks in the skill areas defined under motor and process. The lowest scores is one and the highest score can be four. Each tester who is certified to administer the AMPS has been tested and rated for consistency and reliability.

13. These patients shown in Exhibit C were selected for the study because of their continual cognitive decline prior to the clinical trial in accordance with the present invention. In addition, historical controls with this disease have in general a downward trend that is not seen in these patients.

14. A larger placebo controlled trial of the present invention has been initiated independent of our group at a facility in Western Pennsylvania. Anecdotal and trial data suggest that antibiotics can temporarily improve or stabilize the clinical status of patients with Alzheimer's disease, supporting the idea that Alzheimer's disease pathogenesis may be associated with bacterial infection. That bacterial infection could be caused by a number of

pathogens. This concept is not shown or suggested by any cited prior art. In fact, the present declarant is unaware of any publication which would show or suggest the present invention.

15. Further, no person knowledgeable in the art prior to the present invention would consider using antibiotics, alone or in combination with an anti-inflammatory agent, to treat Alzheimer's disease.

16. Standard treatment of a *C. pneumoniae* respiratory infection with antibiotics would most likely be insufficient to observe improvement in Alzheimer's patients because this bacteria is difficult to clear from tissues and would likely require 3 months of combined antibiotic therapy to see real improvement. Thus, someone attempting to merely eradicate *C. pneumoniae* using standard treatment would not arrive at the success of the present invention in treating Alzheimer's disease. This further demonstrates that the cited prior art does not show any motivation, alone or in combination, to show or suggest the present invention.

17. Several scientists and clinicians have remarked that there is "no evidence that infection plays a role in Alzheimer's disease," this is a quote after a paper on the present invention was published. This statement is attributed to Dr. Selko, who by all measures is an expert in the field of the treatment of Alzheimer's disease. Thus, it is submitted that the present invention is not an obvious modification of the prior art. In a statement by Dr. Khachaturian, former Associate Director for the Neuroscience and Neuropsychology of

Aging Program (NNA) at the National Institution on Aging (NIA), National Institutes of Health (NIH), and the Director of the Office of Alzheimer's Disease Research has stated that "People have been looking at viruses. They haven't been looking at bacteria." Thus, others acknowledge that the concept of the present invention is novel and not shown or suggested by any published references.

18. Regarding the specifically cited prior art, I believe that Shor does not render claims 8-17 *prima facie* obvious. Shor discloses treatment of arterial *Chlamydial* granuloma by administering certain compounds. Shor makes it clear, at column 2, lines 1-2, that tetracyclines and macrolides were well-known art-recognized compounds effective for treatment of *Chlamydia pneumoniae* respiratory infections.

19. Based on these teachings, one of ordinary skill in the art at the time the present invention was made, would not have applied the teachings of Shor to treat Alzheimer's disease because, until the present invention, it was not known that *C. pneumoniae* infection in the CNS was involved in AD pathology such that treating the Chlamydial infection would treat Alzheimer's.

20. These surprising teachings were heretofore unknown and no amount of additional observation of the effects of macrolides and anti-inflammatory agents in arterial *Chlamydial* granuloma patients would have revealed that such treatment would be effective against Alzheimer's disease.

21. The correlation between *Chlamydial* infection in the CNS and Alzheimer's disease could not be predicted based upon the teachings of Shor.

22. Because Shor does not teach or suggest all of the claims limitations, and because there would have been no motivation to apply the teachings of Shor, nor any reasonable expectation of success in doing so, to treat Alzheimer's disease, Shor cannot render the present invention prima *facie* obvious.

23. Further, even assuming, *arguendo,* that the method of Shor would treat a *C. pneumoniae* infection in the CNS, it would not have been obvious to one of ordinary skill that the treatment would thereby treat Alzheimer's disease,

24. Prior to the Applicants' discovery that *C. pneumoniae* infection in the CNS is involved in Alzheimer's pathology, it would not have been obvious to the skilled artisan to look for, much less to treat, a *C. pneumoniae* infection in the CNS where the patient does not present multiple sclerosis or meningoencephalitis symptoms.

25. Therefore, art-recognized methods for treatment of *C. pneumoniae* infection cannot render the present invention *prima facie* obvious where it was <u>not</u> know that *C. pneumoniae* infection could be present in the CNS and, with regard to claims 8-17, where it was not known that *C. pneumoniae* infection in the CNS plays a role in Alzheimer's disease. Assuming, for argument's sake, that it would have been obvious that such an infection would be

present in the CNS and it would have been eve more surprising that treating a *C. pneumoniae* infection in the CNS would treat Alzheimer's disease.

26. For all these reasons, I submit that the presently claimed invention, is now shown or suggested by the cited art.

The undersigned declares further that all statements made herein of his own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful, false statements and the like so made are punishable by fine, or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of any patent issuing therefrom.

Further Declarant sayeth not.

August 6, 2001

J. Todd Abrams

Dr. J. Todd Abrams

CURRICULUM VITAE

ABRAMS, J. TODD, PhD

EDUCATION:

Lafayette College, Easton, PA	1975-1979. B.A. Biology
University of Pennsylvania, Philadelphia, PA	1981-1987. Ph.D. Immunology

COMMUNITY SERVICE

1999-Present	President, Foundation for Research Into Diseases Aging
1997- Present	Member, Golden Slipper Club and Charities

PROFESSIONAL EXPERIENCE

1999-Present	Director, Clinical Program Development, Meniscus Limited, Bala Cynwyd, PA
1998-Present	Research Associate Professor, Philadelphia College of Osteopathic Medicine, Philadelphia, PA
1998-1999	Clinical Associate, Meniscus Limited, Bala Cynwyd, PA
1994-1998	Assistant Professor, Allegheny University of the Health Sciences, Philadelphia, PA
1992-1994	Research Assistant Professor, University of Miami, Miami, FL
1990-1992	Research Associate, Wistar Institute, Philadelphia, PA
1987-1990	Postdoctoral Fellow, Wistar Institute, Philadelphia, PA
1981	Research Technician, Carolinska Institute (Sweden)
1979-1981	Research Technician, Dana Farber Cancer Institute
1974-1975	Research Assistant, Hahnemann Medical College

SCIENTIFIC METHODOLOGIC EXPERIENCE

PCR for detection of eukaryotic, bacterial and viral DNA	RT-PCR for detection of cytokine, bacterial and viral mRNA.	PCR primer development. Designed primers for bacterial and viral genes.	PCR product cloning. Cloned PCR products into TA cloning kit.	Cell Culture. MØ, T-cell, Keratinocyte, hybridoma, astrocytoma ect.	Immunohisto-chemistry. Detection of cell surface antigens and cytokines.
TCL of gangliosides.	Immuno-blotting	Electro-phoresis: SDS-PAGE and Agarose	In-situ hybridization	Proliferation assays	TUNEL assay for apoptosis

PATENTS

1. 284,558: Growth Factor SAF.
2. 09/227,749 Pending: Treatment and Diagnosis of Alzheimer's disease. Balin, Abrams, Whittum-Hudson and Hudson.
3. Provisional: U.S. Patent Application Entitled " Compositions, Methods and Kits for Diagnosis and Treatment of Cutaneous T cell Lymphomas" Abrams and Balin.

GRANT SUPPORT HISTORY

Title: "DHEA and the immunosenescent Th2 cytokines in patients with CTCL."
Source: NIH KO-7 AG 00532-05
Role: Principal Investigator.

Title: "Normal Hematopoietic Cellular Response to Sézary T Cell-Activating Factor".
Source: Concern Foundation for Cancer Research
Role: Principal Investigator

Title: "Characterization of Sézary T cell Activating Factor"
Source: American Cancer Society
Role: Co-Principal Investigator.

Title: Growth Requirements for Cutaneous T cell lymphoma.
Source: National Institutes of Health
Role: Scientist.

PUBLICATIONS:

1. Todd, RF., III, Griffin, JD, Ritz, J, Nadler, LM, **Abrams. JT**, and Schlossman, SF. 1980. Expression of normal monocyte-macrophage differentiation antigens on HL-60 promyelocytes undergoing differentiation induced by leukocyte-conditioned medium or phorbal diester. Leukemia Res. 5:491-495.
2. **Abrams, JT.** 1987. Inhibition of murine mixed lymphocyte responses by gangliosides-isolated from murine antigen presenting cells and spleen cells. Ph.D. Thesis. University of Pennsylvania.
3. **Abrams, JT**, Lessin, S, Ghosh, SK, Ju WD, Vonderheid, EC, Nowell, PC, Murphy, G, Elfenbein, B, and DeFreitas, E. 1991. A clonal CD4 positive T cell line established from the blood of a patient with Sézary syndrome. J. Investig. Dermatol. 96:31-37.
4. **Abrams, JT**, Lessin, S., Ghosh, SK, Nowell, PC, Ju, W, Vonderheid, EC, Rook, A, and DeFreitas, E. 1991. Malignant and non-malignant T cell lines from human T cell lymphotropic virus type I-negative patients with Sézary syndrome. J. Immunol. 146:1455-1462.
5. **Abrams, J.T.**, Ghosh, S.K., and DeFreitas, E. 1993. Sézary T cell activating factor induces functional IL-2 receptors on T cells derived from patients with Sézary syndrome. Cancer Research 53:5501-5506.

6. Ghosh, S. K., **Abrams, J. T.,** Terunuma H.,Vonderheid E. C., and DeFreitas.E. 1994. Human T-Cell Leukemia Virus Type I *tax/rex* DNA and RNA in Cutaneous T-Cell Lymphoma. Blood 84: 2663-2671.
7. Stone, KR, Walgenbach, AW, **Abrams, JT**, Nelson, J, Gillett, N, Galili, U. 1997. Porcine and bovine cartilage transplants in cynomolgus monkey. Transplantation. 63:640-645.
8. Yassin, RR and **Abrams, JT.** 1998. Gastrin induces IP3 formation through phospholipase C gamma 1 and pp60c-src kinase. Peptides 19:47-55.
9. Vonderheid EC, Zhang Q, Lessin SR, Polansky M, Abrams JT, Bigler RD, Wasik MA. 1998. Use of serum soluble interleukin-2 receptor levels to monitor the progression of cutaneous T-cell lymphoma. J Am Acad Dermatol. 38:207-220.
10. Vonderheid EC, Ekbote SK, Kerrigan K, Kalmanson JD, Van Scott EJ, Rook AH, Abrams JT. 1998. The prognostic significance of delayed hypersensitivity to dinitrochlorobenzene and mechlorethamine hydrochloride in cutaneous T cell lymphoma. J Invest Dermatol. 110:946-950.
11. Balin BJ, Gerard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP. 1998. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol (Berl). 187:23-42.
12. LaTemple DC, **Abrams, JT**, Galili U. 1999. Increased immunogenicity of tumor vaccines complexed with anti-Gal: studies in knockout mice for alpha1,3galactosyltransferase Cancer Res. 59:3417-3423.
13. **Abrams JT**; Vonderheid EC; Kolbe S; Appelt DM; Arking EJ; Balin BJ. 1999. Sezary T-cell activating factor is a Chlamydia pneumoniae-associated protein. Clin Diagn Lab Immunol 6:895-905.
14. Arking, EJ, Appelt, DM, Kolby, SJ, Abrams, JT, and Balin, BJ. 1999. Ultrastructural Analysis of Chlamydia pneumoniae in the Alzheimer's brain. Pathogenesis 1:210-211.
15. **Abrams, J.T.**, Balin, B.J., and Vonderheid, E.C. 2001. Association between Sézary T-cell activating factor (SAF), *Chlamydia pneumoniae*, and cutaneous T-cell lymphoma. (In Press) Annals of the New York Academy of Sciences.

Manuscripts in preparation

16. Arking, EJ, Appelt, DM, Abrams, JT, Kolby, SJ, and Balin, BJ. 2001. In situ hybridization of Chlamydia pneumoniae in Alzheimer's Disease. (In preparation: J Histochem Cytochem)
17. Abrams, J.T., Kolby, S.J., Appelt, D.M., Arking, E.J., and Balin, B.J. 2001. Infection of cell lines of neurologic origin with Chlamydia pneumoniae (In preparation for J Infectious Disease).
18. Abrams et al. 2001. Infection of normal human keratinocytes by C. pneumoniae TWAR 183 and potential infection of Cutaneous T cell lymphoma lesions. (In preparation J. Invest. Dermatol.)

Chapters

19. **Abrams, J.T.**, Lessin, S., Ju, W.D., Vonderheid, E.C., Rook, A., Nowell, P.C., Kadin, M., and DeFreitas, E. 1990. Analysis of T cells and long-term lines from patients with Sézary syndrome. In: Human Retrovirology: HTLV. Edited by William Blatner. Raven Press. p 147-161.

Recent Abstracts

20. **Abrams, J. Todd**, Freeman, S., Liao, B., Chapman, M., Kantor, G., Spielvogel, R., and Vonderheid E. C. 1996. Establishment of a whole skin organ culture model of cutaneous T cell lymphoma. J. Investig. Dermatol. 106:879.
21. Boshan, L, Freeman, S., Vonderheid E. C., Chapman M., Kantor, G., Spielvogel, R, and **Abrams, J. T .** 1996. Detection by Immunohistochemistry of T cell markers, proliferation associated antigens, and cytokines in paraffin embedded tissues. J. Investig. Dermatol. 106: 888.
22. Ghosh, S. K., Ghosh, S., **Abrams, J.T.**, DeFreitas, E., Byrnes, J. J. 1996. Detection and expression of endogenous HTLV-I tax/rex gene in cutaneous T cell lymphoma. Blood 88:381a.
23. Balin, B.J., Arking, E.J., Gerard, H.C., Appelt, D.M., Abrams, J.T., Whittum-Hudson, J.A., and Hudson, A.P. 1998. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Soc. Neurosci. Abstr. 24: 775.8.

Anecdotal reports from individuals on antibiotics with Alzheimer's Disease.

The following summaries are based on reports, both verbal and written accounts, of a number of individuals in communities across the US who have first-hand knowledge of a loved one who has experienced some level of improvement of their Alzheimer's Disease following treatment with antibiotics. In some cases, individuals have pursued this course of therapy based on the early work of Balin et al., 1998 who have identified C. pneumoniae in the brains of Alzheimer individuals at autopsy. At present, the diagnosis of Alzheimer's alone has led many individuals to try antibiotic approaches eventhough they may not have been diagnosed as having an infection with C pneumoniae. The rationale for this regimen comes from the frustration of not having efficacious treatment modalities at this time for this progressive neurodegenerative disease.

Case 1

Mary M. is a 66 year old white female who was diagnosed with Alzheimer's Disease in May 1998. In January of 1999, her husband contacted me after having read a report on our findings from the November 1998 annual Society for Neuroscience meeting. He wanted to know if I could advise them on what type of antibiotic regimen could be used for treating his wife's Alzheimer's disease. I informed him at that time that I was not a physician and could not prescribe antibiotics, although I was aware that macrolide antibiotics were being used to treat Chlamydial infections. Without knowing whether or not Mary was infected with C pneumoniae in her brain, her husband wanted to give it a try in having her treated with an antibiotic regimen. In February of 1999, Mary started a course of antibiotic treatment with a macrolide antibiotic. She continued on the antibiotic therapy with periodic on/off cycles for the next 3 months during which time she improved quite substantially in her cognitive functioning. Her husband recounted that she went from scoring 17 out of 30 on the Mini Mental State Exam (MMSE) test to a 30/30 on the same test following this course of treatment. This was astounding to us, but provided some hope that we could treat some people with Alzheimer's Disease with antibiotics and obtain some recovery of function. Interestingly, Mr. M. sent a recent report to Dr. Balin on the most recent MRI exam performed on Mary M. The MRI results indicate that the atrophy found in Mary's brain 1 year prior by MRI had not significantly changed over the course of the past year. In addition, Mary M., according to her husband appears to be very stable with regard to her cognitive functions.

Case 2

Meta T. is an 88 year old women who has had a diagnosis of Alzheimer's disease for approximately 9 and ½ years. Her daughter Shirley K. first contacted me in February of 1999 after having read of my research in the LA Times in which the reporter chronicled our C pneumoniae and Alzheimer Disease findings and report from the Society of Neuroscience Meeting from November 1998. She recounted to me that her mother, Meta T. was noted to improve cognitively (very verbal, appropriate responses in conversation, name recall, etc) upon being treated with Rocephin (a cephalosporin) for a bout of pneumonia from October of 1998. She also stated that the effect of the antibiotic appeared to be helpful for a number of months. Shirley K. tried to persuade the physicians treating her mother that just maybe antibiotics made her mother's Alzheimer's Disease better because of the findings of Balin et al. in 1998. The physicians at that time felt the "risk to benefit ratio" was too great to continue her mother on longterm antibiotic usage. Approximately in May 1999, Shirley K.corresponded with Dr. Balin for advice on use of antibiotics to treat her mother. Apparently, the effects of Rocephin were wearing off and her mother was deteriorating cognitively (not responsive, inattentive). Following conversations with Dr. Balin, Shirley K. convinced the physicians at the nursing home in which Meta T. resided to put her on a course of Zithromax for her Alzheimer's Disease. In August of 1999, Shirley K. wrote to Dr. Balin and included excerpts from conversations with her mother, Meta T. that demonstrated that Meta, had indeed, started to improve again cognitively and was asking and answering questions appropriately.

Case 3

From: Kathy S[redacted]
To: staff.GWIA("BALINB@wpo.auhs.edu","balin@auhs.edu")
Date: 11/1/98 2:54AM
Subject: Alzheimer's article

Dear Dr. Balin:

My brother sent me a copy of an article about your research regarding Alzheimer's link to a bacterium - Chlamydia pneumoniae. It was very interesting to us since WE have been trying to tell my dad's doctor that when he was on an antibiotic for a urinary tract infection, his mind was much clearer. He could carry on a conversation on the phone and remember scores from sports games he had watched. It was unusual. After he was off the medicine, he reverted right back to the way he was. He was especially clear when he was on Bactrim prophylactically (one a day for a month) because he couldn't seem to get rid of whatever infection was making him so weak. I was told that it was because his body wasn't fighting the infection, that his mind could think better. If the urinary infection (if it really was) was gone after the antibiotic was over, then why did his memory revert if he was physically feeling better?

I also met another person who brought this up at a Parkinson symposium in Rochester whose mother was better with her Alzheimer's when she was on an antibiotic for her ear infection. She was practically laughed out of the place but I have her name and address.

Both our parents have PArkinson's and Alzheimer's. My dad is responding to the Aricept but not as well as he used to. Lately, he has had many bad days. I believe you may have the reason that these cells are being damaged in the brain and I applaud you for thinking so far above your colleagues. You don't happen to have a doctor named Siderowf in Pennsylvania, do you? He used to be my dad's neurologist.

Anyway, I would appreciate any copies of your research results that you could e-mail to me so that I could show them to my dad's current doctor and share them with my friend whose mom is also ill. We would also be interested in what antibiotic would most effectively kill this bacteria.

Sincerely,
Kathy S[redacted]

CC: [redacted]

Ref 4

November 22, 1998

Dear Dr. Balin,

I am writing to encourage you in your research regarding the possibility of an infectious agent in Alzheimer's Disease. My mother suffered from this disease for nearly thirteen years. She was part of a longitudinal study at the University of Washington. In the course of taking care of her, I first became the family researcher, then began documentation of her illness. I have written a case study of Alzheimer's (still looking - desperately - for a publisher).

The other day I saw an article in our local paper about your work. I cut it out and handed it to my husband. Said I, "Of all the articles I've seen about this disease, this is the one that excites me most." The reason, Dr. Balin, is that while my mother was being treated for a series of bladder infections, we came upon an antibiotic, Maxaquin, that caused the most amazing changes in her cognitive behavior. I reported these to the University of Washington, as well as to her personal physician. I even asked her physician to leave her on the medication after the bladder infection was gone the second time she was treated with this drug. The doctor did not feel she could ethically do that.

I have attached a few pages from my book to give you an idea of what we saw. I could have her physician send further documentation of mother's treatment for the bladder infections to you if you are interested. On the book pages, (p. 118-121) I have included some marginal notes to orient you. Also, in writing the book, I used my journal entries, in italics.

Again, I am very excited about your work. I know in science one can't make great leaps, but I'd just love to see the before and after psychometric tests on a group of Alzheimer's patients on about a month's worth of Maxaquin! Good luck with your research, and Godspeed.

Sincerely,

Charlotte A

Email

Started Tx: November 16, 1999

Introduction:
JM is a 78 year old white female who presented to her doctor's office with a history of Alzheimers disease (AD). Her family had heard about research being conducted at the Philadelphia College of Osteopathic Medicine, which associated AD with chlamydia pneumonia in the brain. Her family was asking for her to be put on a six month course of Zithromax as per the PCOM group.

History:
In 1996 JM began to experience symptoms of early dementia. She would frequently become lost in areas familiar to her for over fifty years, and misplace items important to her. By September 1999, she was experiencing advanced dementia. She had forgotten her husband of 55 years, her seven children, the house she lived in, and had become somewhat non-conversational, with frequent episodes of agitation.

PMH: MI – June '98
CAD
HTN – controlled with meds
Gastritis
MVA – 1986
Syncopal episode – fell from a stool, head trauma 1989
Incontinence

Medications:
ASA 325 mg daily
Lorazepam 0.5mg BiD
Captopril 12.5 mg ½ tab BiD
Famotidine 20mg BiD
Paxil 20mg daily
Metoprolol 50 mg ¼ tab BiD
Estradiol 2 mg 1 daily
Aricept
HCTZ 50mg ½ tab daily

On her first visit a mini mental status exam (MMSE) was attempted with minimal success. The patient was unable to determine the day of the week, month of the year, or keep up with current events. She was unable to name the President. She had a somewhat limited recall of long term events; she was unable to remember her wedding anniversary date. Serial 7's were attempted – she was able to do one subtraction and then she completely lost tract. She was unable to complete the entire mental exam. A score of less than 10/30 on the MMSE can be assumed, indicating severe dementia. Her daughter and caregiver report that she gets lost and turned around frequently, even in her home of 50 years. She frequently thinks that her husband is her father, who died in the 1950's. She often does not recognize her children and will ask them how their mother is doing. She requires assistance in taking her medications and in general daily living – cooking,

driving, and decision making. She is able to perform most activities of daily living on her own. (Bathroom - once told where the bathroom is, dressing - once the clothes are laid out for her, and showering) She has an extremely limited short term memory and attention span. She frequently becomes agitated.

The clinical trial from PCOM consisted of putting the patient on Azithromycin 250 mg daily for 9 months. She was started on the treatment on Nov 16, 1999. Within 3 weeks her family reported seeing a significant change in her personality. She became more interactive with family members. By Thanksgiving, Nov 27, she was able to recognize her husband and children, and would comment on how much better she felt. She often commented on how she knew she could remember more now. Over the next five months she continued to improve. She began to find items she had lost months before. Her family says that she 'got her personality back.' She laughs and jokes with people, whereas before she was depressed and would often stare blankly. She now has a longer attention span, and is able to spend several hours putting puzzles together or gardening.

She still has episodes of dementia, particularly when she gets tired and is off of her normal routine. She occasionally confuses the past and the present, but now she realizes her mistake and corrects herself.

A mini mental status exam was done in Jan. She scored a 16, showing improvement but still significant dementia. There has been an improvement in her drawing a clock face. When she was initially asked to draw a clock, she drew a square with no numbers. Now she draws a circle with the number 12 at the top, and the numbers 13-20 continuing around the clock.

Physical Exam:

General:	Obese female, appearing stated age. No acute distress.
Vitals:	Vital signs stable
HEENT:	PERRLA, EOMI, TM clear, MMM, NC/AT
Neck:	Supple, no lymphadenopathy, no JVD, no bruit
Heart:	Regular, II/VI SEM
Lungs:	CTA bilat
Abdomen:	Soft, NT/ND, + bowel sounds, no organomegaly, no masses
Extremities:	No C/C/E, + distal pulses
Skin:	Warm/dry

Discussion:

Three years ago when JM was diagnosed with dementia she began the slow, steady, unrelenting course associated with Alzheimers disease. Despite her treatment with Aricept, she continued to deteriorate. Within one week of being started on Zithromax there was a noticable difference in JM. She was more alert, had an increased short term memory, and was more interactive with family members. She continued to improve with her progress eventually leveling off. She still gets lost at times, particularly when she is tired or out of her home environment. She is not able to drive or stay home alone, mainly for fear that something might happen.

The biggest change has been in her relationships with her family, and in a marked decrease in agitation. Although she still shows some signs of dementia, she is not as

advanced now as she was one year ago, and she is better than she was three years ago according to her care giver.

She has been finished with the treatment for approximately one month. She has shown no signs of decline or increased dementia. Last week she was visiting her daughter when she noticed that her daughter was wearing an outfit that she had out-grown a year or so ago. She commented that she remembered it and knew it was hers. Then later she said 'I'll take my outfit back any time.'

She has a history of athersclerosis and myocardial infarction, also associated with *Chlamydia pneumonia*. It is possible that the trauma she suffered during a MVA could have disrupted the blood brain barrier, allowing for the organism to cross into her brain.

Conclusion:

I know this case well because JM is my grandmother. I am a 4th year medical student at PCOM. The changes seen in her are unlike anything I have seen or heard of in an Alzheimer's patient. The process of Alzheimer's does not reverse itself...ever, and nothing currently on the market is able to produce these kinds of results. After being off of the antibiotic for some time she has begun to show signs of decline again. We plan on restarting her on Zithromax or another antibiotic in the hopes of dramatic results once again.

Effect of Azithromycin on Progression of Alzheimer's Disease: Pilot Study

Participant #1 - W.S.

	MMSE	GDS	AMPS (Aggregate)	
			Task #1	Task#2
Initial 11/17/99	24/30	0	Motor – 53 Process - 42	44 49
90 days 2/16/00	22/30	2	Motor - 52 Process - 57	53 63
180 days 5/19/00	25/30	4	Motor - 54 Process - 42	54 45

*MMSE score declined at 90 day testing, but improved to above initial score at 180 days.

*AMPS Motor scores remained fairly consistent throughout the 3 test dates, but AMPS Process scores declined significantly between the 2nd and 3rd test dates (compare number of Markedly Deficient areas in the Summary Reports)

Effect of Azithromycin on Progression of Alzheimer's Disease: Pilot Study

Participant #2 – D. D.

	MMSE	GDS	AMPS (Aggregate)
			Task #1 Task#2
Initial 4/19/00	15/30	4	Motor – 60 62 Process - 72 72
90 days 7/23/00	17/30	2	Motor - 60 61 Process – 70 59
180 days 10/11/00	16/30	1	Motor - 61 60 Process - 70 66

*MMSE score improved from Initial to 90 day Assessment, and then a slight decline at 180 day Assessment

*GDS improved from Initial to 90 day, and again from 90 day to 180 day.

AMPS scores remainder relatively consistent

Effect of Azithromycin on Progression of Alzheimer's Disease: Pilot Study

Participant #3 – A. S.

	MMSE	GDS	AMPS (Aggregate)
			Task #1 Task#2
Initial 4/19/00	21/30	3	Motor – 46 51 Process - 58 63
90 days 7/19/00	21/30	2	Motor - 43 43 Process - 56 48
180 days 10/11/01	19/30	8	Motor - 57 56 Process - 68 67

*MMSE score remained the same from Initial to 90 day Assessment, then slightly declined at 180 day Assessment

*GDS improved from Initial to 90 day, then declined by 180 Day

AMPS Motor score fluctuations appear related to exacerbation of respiratory difficulties. Was having more difficulty breathing at 90 day Assessment than at other times.